Notice of Allowability	Application No.	Applicant(s)	
	10/741,657	LAW ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *14 March 2007*.

2. ☒ The allowed claim(s) is/are *71-85 and 88-92*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20070509* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

2. Authorization for this examiner's amendment was given in a telephone interview with Susan Harlocker on May 15, 2007.

3. The application has been amended as follows:

In the specification:

The paragraph beginning at line 25 of page 10 has been replaced with the following paragraph:

In many preferred uses of the present invention, including *in vivo* use of the GPR64 antibodies in humans for and *in vitro* detection assays, it may be preferable to use chimeric, ~~primatized~~ Primatized™, humanized, or human antibodies.

The paragraph beginning at line 21 of page 12 has been replaced with the following paragraph:

The term "~~primatized~~ Primatized™ antibody" refers to an antibody comprising monkey variable regions and human constant regions. Methods for producing ~~primatized~~ Primatized™ antibodies are known in the art. See e.g., U.S. Pat. Nos. 5,658,570; 5,681,722; and 5,693,780, which are incorporated herein by reference in their entireties.

The paragraph beginning at line 17 of page 14 has been replaced with the following paragraph:

The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that arc the same (i.e., about 60% identity, preferably 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection ~~(see, e.g., NCBI web site www.ncbi.nlm.nih.gov/BLAST/ or the like)~~. Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions, as well as naturally occurring, e.g., polymorphic or allelic variants, and man-made variants. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

The paragraph beginning at line 22 of page 15 has been replaced with the following paragraph:

Preferred examples of algorithms that are suitable for determining percent sequence identity and sequence similarity include the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., Nuc. Acids Res. 25:3389-3402 (1977) and Altschul et al., J. Mol. Biol. 215:403-410 (1990). BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is

publicly available through the National Center for Biotechnology Information (~~www.ncbi.nlm.nih.gov/~~). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, e.g., for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

The paragraph beginning at line 3 of page 17 has been replaced with the following paragraph:

A "host cell" is a naturally occurring cell or a transformed cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be cultured cells, explants, cells in vivo, and the like. Host cells may be

prokaryotic cells such as E. coli, or eukaryotic cells such as yeast, insect, amphibian, or mammalian cells such as CHO, HeLa, and the like (see, e.g., the American Type Culture Collection catalog ~~or web site, www.atcc.org~~).

The paragraph beginning at line 17 of page 29 has been replaced with the following paragraph:

Once the GPR64 protein is produced, it is used to generate antibodies, e.g., for immunotherapy or immunodiagnosis. In some embodiments of the invention, the antibodies recognize the same epitope as the CDRs shown in Table 2. The ability of a particular antibody to recognize the same epitope as another antibody is typically determined by the ability of one antibody to competitively inhibit binding of the second antibody to the antigen. Any of a number of competitive binding assays can be used to measure competition between two antibodies to the same antigen. An exemplary assay is a Biacore™ assay as described in the Examples, below. Briefly in these assays, binding sites can be mapped in structural terms by testing the ability of interactants, e.g. different antibodies, to inhibit the binding of another. Injecting two consecutive antibody samples in sufficient concentration can identify pairs of competing antibodies for the same binding epitope. The antibody samples should have the potential to reach a significant saturation with each injection. The net binding of the second antibody injection is indicative for binding epitope analysis. Two response levels can be used to describe the boundaries of perfect competition versus non-competing binding due to distinct epitopes. The relative amount of binding response of the second antibody injection relative to the binding of identical and distinct binding epitopes determines the degree of epitope overlap.

The paragraph beginning at line 21 of page 35 has been replaced with the following paragraph:

Binding affinity for a target antigen is typically measured or determined by standard antibody-antigen assays, such as Biacore™ competitive assays, saturation assays, or immunoassays such as ELISA or RIA.

The paragraph beginning at line 7 of page 42 has been replaced with the following paragraph:

The biotinylated targets were hybridized to the Eos Hu03, a customized Affymetrix™ GENECHIP® (Affymetrix, Santa Clara, Calif.) oligonucleotide array comprising 59,619 probesets representing 46,000 unique sequences including both known and FGENESH predicted exons that were based on the first draft of the human genome. The Hu03 probesets consist of perfect match probes only, most probesets having 6 or 7 probes. Hybridization signals were visualized using phycoerythrin-conjugated streptavidin (Molecular Probes, Eugene, Oreg.).

The paragraph beginning at line 18 of page 46 has been replaced with the following paragraph:

Mice were immunized with a GPR64-Fc fusion protein. The fusion construct linked amino acids 1-588 of the full-length GPR64 sequence (SEQ ID NO:2) to an Fc protein. Spleen cells were fused and the original hybridomas were screened initially by FACS and ELISA, and later for proliferation effects, IHC on frozen tissue sections, and for off-rate binding kinetics. Approximately 40 clones were selected for subcloning based on tight binding and low off-rate. The subclones were expanded and purified. The purified monoclonal antibodies were then compared with one another by FACS titration, immunofluorescence and Biacore™ and assessed for in vitro and vivo effects on proliferation.

The paragraph beginning at line 27 of page 46 has been replaced with the following paragraph:

Cells were removed with 5 mM EDTA in Tris-HCl (pH 8.0) and blocked by centrifugation in HBSS containing 3% heat-inactivated FBS, 1% normal goat serum (Sigma), and 1% BSA at 4° C for 5 min. Cells were incubated for 1 h at 4° C. with anti-GPR64-FITC (10 μg/ml; R&D Systems) in FACS buffer (PBS containing 0.1% BSA). Excess mAb was removed by centrifugation, and cells were resuspended in FACS buffer containing propidium iodide (1 μg/ml). Fluorescence intensity was measured on a FACScan (Becton Dickinson). Quantitative FACS was performed in a similar manner, except that a saturating concentration of anti-GPR64-FITC (50 μg/ml) was used on cells and similarly treated Quantum Simply Cellular™ beads (Sigma), a mixture of four populations of agarose beads of known antibody binding content. Antibody binding site quantification was performed by comparing the MFI of each cell line with that of the Quantum Simply Cellular™ bead populations and were corrected for nonspecific effects as described (Brockhoff et al., 1994, Cytometry 17: 75-83). Experiments were performed twice in triplicate.

The paragraph beginning at line 11 of page 47 has been replaced with the following paragraph:

Kinetics measurements between human GPR64-Fc fusion protein and GPR64 monoclonal antibodies were performed using Biacore™ 3000 (BIAcore, Sweden). Anti-GPR64 mAbs were immobilized with 100 RUs on Research-grade CM5 sensor chip by the Biacore™ amine coupling reagents (N-ethyl-N'-dimethylaminopropylcarbodiimide, EDC; N-hydroxysuccinimide, NHS; and ethanolamine HCl, pH8.5). Assays were run at a flow rate of 30 μl/min at room temperature. Three-minute association phase of each GPR64-Fc was followed by ten-minute injection of running buffer (10 mM Hepes, 300 mM sodium chloride, 3 mM EDTA, 0.05% P-20, pH7.4) to monitor dissociation. The mAb surface was regenerated with 25 mM NaOH. The binding kinetics of each GPR64-mAb pair was calculated from the data at six different concentrations (2048 nM, 512 nM,

128 nM, 32 nM, 8 nM, 2 nM) of GPR64-Fc analyte, using the BIAevaluate program. Double referencing was applied in each analysis to eliminate background responses from reference surface and buffer only control. The affinity (K_D) of binding was obtained by simultaneously fitting the association and dissociation phases of the sensorgram from the analyte concentration series using the bivalent analyte model from BIAevaluate software.

The paragraph beginning at line 27 of page 47 has been replaced with the following paragraph:

Cells grown on coverslips were chilled on ice in growth medium for 10 min. Growth medium was replaced with medium containing anti-GPR64 mAb (10 μg/ml) at 4° C. for 1 h. Antibody binding was detected using AlexaFluor-488 goat anti-mouse secondary antibody (1:2200 dilution in chilled growth media; Molecular Probes). Cells were washed three times with PBS, fixed using 5% UltraPure Formaldehyde in PBS for 40 min and washed two additional times using PBS. Slides were mounted using Permafluor™ (Coulter) for visualization.

The paragraph beginning at line 11 of page 48 has been replaced with the following paragraph:

Cell lines were plated at a density of 2500 cells/well in 96-well plates and allowed to recover overnight in phenol red-free Iscove's modified Dulbecco's medium (IMDM) containing 10% FBS and supplements (growth medium). Cells were challenged for 1 h with mAb or ADC (twice in a volume of 50 μl) in IMDM at the indicated concentrations. Cells were then washed twice with growth medium and allowed to proliferate in fresh growth medium for 4 days, cell viability was then assessed by the CellTiter 96™ AQueous Non-Radioactive Cell Proliferation Assay (Promega), as per the

manufacturer's instructions. All growth studies were performed at least three times in triplicate.

The paragraph beginning at line 20 of page 48 has been replaced with the following paragraph:

FIG. 5 depicts a table showing the compiled results on 42 mAbs (including GPR64-18 described in Example 2). The results include various measures of antibody binding affinity including FACS titration (i.e. EC_{50}), surface plasmon resonance (i.e. Biacore™), immunohistochemical (IHC) and immunofluorescence (IF). Interestingly, many of these monoclonal antibodies are IgG2a and IgG2b isotype. More importantly, many of these antibodies exhibit low EC_{50} values by FACS assay, and nanomolar or subnanomolar K_D values by Biacore™.

The paragraph beginning at line 8 of page 50 has been replaced with the following paragraph:

Epitope mapping was performed by competitive FACS assay. Briefly, H460 cells were incubated with 25 μg/ml unlabeled antibody for 1 hr on ice, at which time various amounts of FITC labeled antibody was added. After 30 additional minutes, cells were washed one time and fluorescence was measured by flow cytometry. All data was confirmed by Biacore™.

The paragraph beginning at line 29 of page 51 has been replaced with the following paragraph:

All UniGene™ cluster identification numbers and accession numbers herein are for the GenBank™ sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. GenBank™ is known in the art, see, e.g., Benson, D A, et al., Nucleic Acids Research 26:1-7 (1998). Sequences are also

available in other databases, e.g., European Molecular Biology Laboratory (EMBL) and DNA Database of Japan (DDBJ).

In the claims:

The claims have been replaced with the following set of claims:

Claims 1-70. (Cancelled)

Claim 71. (Previously Presented) A hybridoma cell line deposited as ATCC Accession Number PTA-5704.

Claim 72. (Previously Presented) An antibody produced by the hybridoma cell line of claim 71.

Claim 73. (Currently Amended) ~~The antibody of claim 72, wherein the antibody is an antibody~~ An antigen binding fragment of the antibody of claim 72.

Claim 74. (Currently Amended) The ~~antibody~~ antigen binding fragment of claim 73~~, wherein the fragment is~~ selected from the group consisting of Fab, Fab', $F(ab')_2$, and Fv fragments~~, rIgG, diabodies, single chain antibodies, and multispecific antibodies~~.

Claim 75. (Currently Amended) ~~The~~ A conjugate comprising the antibody of claim 72, wherein the antibody is conjugated to an effector moiety.

Claim 76. (Currently Amended) The ~~antibody~~ conjugate of claim 75, wherein the effector moiety is selected from the group consisting of: a fluorescent label, a radioisotope and a cytotoxic agent.

Claim 77. (Currently Amended) The ~~antibody~~ conjugate of claim 76, wherein the cytotoxic agent is selected from the group consisting of: diphtheria A chain, exotoxin A chain, ricin A chain, abrin A chain, curcin, crotin, phenomycin, ~~neomycin~~ neomycin, and auristatin.

Claim 78. (Currently Amended) The ~~antibody~~ conjugate of claim 77, wherein the cytotoxic agent is auristatin.

Claim 79. (Currently Amended) The ~~antibody~~ conjugate of claim 76, wherein the radioisotope is selected from the group consisting of ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{125}I, ^{131}I, ^{90}Y and ^{186}Re.

Claim 80. (Currently Amended) The antibody of claim 72 ~~or 75~~, wherein the antibody binds a polypeptide having the amino acid sequence of SEQ ID NO:2.

Claim 81. (Currently Amended) The antibody of claim 80, wherein the polypeptide is ~~on~~ localized to the cell surface of a cancer cell.

Claim 82. (Previously Presented) The antibody of claim 81, wherein the antibody inhibits growth of the cancer cell.

Claim 83. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the antibody of claim 72.

Claim 84. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable excipient and the ~~antibody~~ conjugate of claim 78.

Claim 85. (Previously Presented) An antibody produced by a hybridoma cell line having ATCC Accession number PTA-5704.

Claims 86 and 87. (Canceled)

Claim 88. (New) A diabody comprising a first polypeptide comprising the heavy chain variable domain (V_H) of the antibody of claim 72 and further comprising a second polypeptide comprising the light chain variable domain (V_L) of the antibody of claim 72, wherein said diabody comprises an antigen binding domain that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

Claim 89. (New) A single chain antibody comprising the heavy chain variable domain (V_H) of the antibody of claim 72 and the light chain variable domain (V_L) of the antibody of claim 72, wherein said single chain antibody binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

Claim 90. (New) A chimeric antibody comprising a first polypeptide comprising the heavy chain variable domain (V_H) of the antibody of claim 72 and further comprising a second polypeptide comprising the light chain variable domain (V_L) of the antibody of claim 72, wherein said chimeric antibody binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

Claim 91. (New) A humanized antibody comprising a first polypeptide comprising each of the three complementarity determining regions (CDRs) of the heavy chain variable domain (V_H) of the antibody of claim 72 and further comprising a second polypeptide comprising each of the three CDRs of the light chain variable domain (V_L) of the antibody of claim 72, wherein said humanized antibody binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

Claim 92. (New) The conjugate of claim 75, wherein the antibody binds a polypeptide having the amino acid sequence of SEQ ID NO: 2.

Examiner's Statement of Reasons for Allowance

4. The following is an examiner's statement of reasons for allowance:

The prior art does not teach or fairly suggest a monoclonal antibody produced by the deposited hybridoma having the ATCC accession number PTA-5704, which binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. Accordingly, the prior art does not teach or fairly suggest an antigen binding fragment of this monoclonal antibody, nor does it teach or fairly suggest a recombinant antibody, such a humanized antibody, which is derived from this monoclonal antibody, comprises at least the three CDRs of both the heavy and light chains of the monoclonal antibody, and retains the ability to bind to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

Support for the amendment to the claims is found throughout the specification, as filed. More particularly, with regard to claims 73-80 and 92, support is found, for example, in the original claims. Support for claim 81 is found, for example, at page 41, liens 23-26, as well as the original claims (e.g., claim 10). Support for claim 88 is found, for example, at page 4, lines 28-30; page 8, line 27, through page 9, line 11; and original claim 33. Support for claim 89 is found, for example, at page 6, lines 7-10; page 10, lines 5-8; and original claim 7. Support for claim 90 is found, for example, at page 10, line 25, through page 11, line 6; and original claim 8. Support for claim 91 is found, for example, at page 11, lines 7-29; and original claim 8.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

6. Claims 71-85 and 88-92 have been allowed.

7. Claims 71-85 and 88-92 have been renumbered as claims 1-20, respectively.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
May 15, 2007